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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/799,540	DAVID, NATHANIEL E.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 39-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-38 and 58-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-72* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Bridget E. Bunner.

Status of Application, Amendments and/or Claims

The amendment of 24 July 2006 has been entered in full. Claims 27 and 62 are amended.

This application contains claims 1-19 and 39-57 drawn to an invention nonelected without traverse in the communication of 13 December 2005.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20-38 and 58-72 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to claims 27 and 62 as set forth at pg 2 of the previous Office Action (24 January 2006) is *withdrawn* in view of the amended claims (24 July 2006).

2. The rejection of claims 20-38 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pg 5-7 of the previous Office Action (24 January 2006) is *withdrawn* after further consideration by the Examiner.

3. The rejection of claims 20-21, 26-37, 58, 59, and 61-72 under 35 U.S.C. § 103(a) as set forth at pg 7-9 of the previous Office Action (24 January 2006) is *withdrawn* after further consideration by the Examiner.

4. The rejection of claims 20-25 and 58-60 under 35 U.S.C. § 103(a) as set forth at pg 9-10 of the previous Office Action (24 January 2006) is *withdrawn* after further consideration by the Examiner.

5. The supplemental information disclosure statement filed on 11 August 2006 has been considered.

Claim Rejections - 35 USC § 112

6. Claims 20-38 and 58-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for decreasing coloration of a dermal region comprising administering to said region an effective amount of macrophage colony stimulating factor in conjunction with laser therapy, does not reasonably provide enablement for a method for altering coloration of a dermal region comprising administering to said region an effective amount of a tumor necrosis factor or any other cytokine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 2-5 of the previous Office Action.

Applicant's arguments (24 July 2006), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the burden in presenting a *prima facie* case of non-enablement has not been met. Applicant argues that it is well established that compliance with the enablement requirement does not turn on whether an example is disclosed and cites *In re Borkowski* 422 F2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Applicant contends that in the present case, the specification clearly points out how the cytokine or tumor necrosis factors alter coloration of a dermal region. At pg 10 of the Response, Applicant argues that there is not reason stated by the Examiner to support the assertion that "unpredictability in factors involved in pigmentation and proliferation of melanocytes" would hence require undue experimentation for a person of skill in

the art to be able to use the invention. Applicant submits that the disclosure contains sufficient contend for a person of skill in the art to use the invention without undue experimentation. Applicant cites MPEP §2164.01.

Applicant's arguments have been fully considered but are not found to be persuasive. In the previous Office Action of 24 January 2006, the Examiner made a *prima facie* showing that the scope of the claimed invention is not enabling and provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing (see pages 3-5).

Although Applicant needs to not actually have reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). The Examiner's indication of the absence of a working example is only one facet of the Wands factors, which were provided in the previous Office Action (24 January 2006). Furthermore, although the prophetic example at pg 9-12 of the specification discloses a method for the local and direct administration of cytokines to alter skin coloration, it is not disclosed in a manner such that one skilled in the art could perform the method without undue experimentation. For instance, the specification and the art disclose a large number cytokines that are encompassed in the claimed methods (see pg 9-10; Fitzgerald et al. (2001) The Cytokine FactsBook, London: Academic Press, Table of Contents). However, there is little guidance provided in the specification as to the nexus between all possible cytokines and the alteration of coloration of a dermal region. For example, do the cytokines increase or decrease coloration of the dermal region? Are particular cells intended to be activated by the cytokines? Are certain immune responses, such as inflammation, intended to be activated by the cytokines? Undue experimentation would be

required of the skilled artisan to screen all possible cytokines for color altering activity of a dermal region alone and in conjunction with all possible color alteration treatments, such as laser therapy. One skilled in the art would not be able to predict that all cytokines would be able to alter skin coloration because cytokines have diverse physiological functions and act on different cell types (Elgert, K.D. (1996) Immunology, understanding the immune system. New York: Wiley-Liss, Inc., pg 200-201, 215).

Furthermore, the instant specification and relevant literature teaches that fibroblasts and macrophages take up and store ink particles from tattoos (see for example, bottom of pg 4 of the specification; Adatto, M.A. Med Laser Appl 19: 175-185, 2004; pg 176, col 2, pg 177, col 1; Kilmer et al. "Tatto Lasers", http://www.emedicine.com/derm/topic563.htm, 25 May 2006, pg 2-3). However, after laser treatment, fragmentation of tattoo pigment and engulfment by macrophages occurs (Adatto, pg 177, col 1; Kilmer pg 6-14). Thus, as disclosed by Cohen et al., the delivery of macrophages to the laser-treated region could enhance tattoo removal (pg 84, col 1, 3rd full paragraph). However, regarding claims 20-38 and administration of a TNF, the state of the art is such that TNF-α, an inflammatory cytokine, does not effect phagocytosis of cultured peritoneal macrophages (Smith et al. J Neurosci Res 54: 68-78, 1998 ; pg 69, bottom of col 1 ; pg 70, bottom of col 2 through pg 71, col 1; Fig 2A). Manaka et al. also teaches that *hyperpigmentation* in seborrhoeic keratosis, a benign epidermal tumor with increased pigmentation, has *increased* expression of TNF-α (Brit J Dermatol 145: 895-903, 2001; abstract, Figure 8). Thus, one skilled in the art would not predict that administration of a tumor necrosis factor, such as TNF-α, would reduce the coloration of a dermal region on a subject.

It is noted that the fact pattern of the case cited by the Applicant (*In re Borkowski*) and

the fact pattern of the instant rejection are significantly different, and the court decision is not binding with regard to the instant rejection. For example, in *Borkowski*, the claims are drawn to a process for producing oxygenated hydrocarbons. The Court of Customs and Patent Appeals indicated that the specification need not contain a working example if one skilled in the art could practice it without undue experimentation and considering the nature of the claimed invention (process for producing hydrocarbons), the few hours of experimentation required were not an undue amount of time. However, in contrast to *Borkowski*, more than a few hours of experimentation are required to generate the claimed invention of the instant application.

A specification may be enabling even though some experimentation is necessary, but the amount of experimentation, however, must not be unduly extensive. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily alter coloration of a dermal region comprising administering a tumor necrosis factor or any other cytokine (except macrophage colony-stimulating factor).

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to screen all possible cytokines for color altering activity (either enhancement or inhibition) of a dermal region *alone and in conjunction with* all possible color alteration treatments, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art (see Smith et al., Manaka et al.), the unpredictability of the effects of the administration of all possible cytokines to a dermal region, and the breadth of the claims which are directed to all possible cytokines, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 58-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 5-7 of the previous Office Action (24 January 2006).

Applicant's arguments (24 July 2006), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant argues that the Examiner has failed to rebut the presumption that "a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention". Applicant contends that the description of cytokines and

tumor necrosis factors in the disclosure does provide a precise definition that a person of skill in the art would recognize and understand, e.g. a chemical name. Applicant submits that there is no ambiguity about the identity of a substance referred to. Applicant argues that "interleukins, lymphokines, tumor necrosis factors, interferons, chemokines, and growth factors are well recognized and well defined names or nomenclature for cytokines by a person of skill in the art.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, at pg 9-10 ([0028-0034]) of the specification, a few examples of cytokines are disclosed. However, interleukins, lymphokines, tumor necrosis factors, interferons, chemokines, and growth factors further encompass a large number of proteins (see for example Fitzgerald et al. (2001) The Cytokine FactsBook, London: Academic Press, Table of Contents). The description in the specification of a few examples of cytokines is not adequate written description of an entire genus of methods of using cytokines. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. However, in the instant application, there is not even identification of any particular function of the cytokines that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of methods utilizing the genus of cytokines.

In *University of Rochester v. G.D. Searle & Co,* the U.S. Court of Appeals Federal

Circuit found that a patent directed to method for inhibiting prostaglandin synthesis in a human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, is subject to the written description requirement. Although the instant application provides a few examples of cytokines that could be used in the claimed method for altering coloration of a dermal region, the evidence does not demonstrate that the skilled artisan would be able to envision the detailed structure and function of the numerous cytokines encompassed by the claims. The written description requirement the requirement must still be met in some way so as to describe the claimed invention to "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 at 1116).

Therefore, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of methods utilizing the genus of cytokines.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 20 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Jensen et al. (J Clin Invest 104: 1761-1770, 1999).

Jensen et al. teach the topical administration of tumor necrosis factor to skin wounds of hairless mice after experimental injury (abstract; pg 1763, col 1, 1st full paragraph).

9. Claims 20, 29, 30, 58, 64, and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Foldvari et al. (U.S. Patent 6,165,458).

Foldvari et al. teach the topical and transdermal administration of a cytokine, wherein the cytokine is conjugated to at least one fatty acid moiety (col 1, lines 49-56; col 2, lines 1-18; col 10).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
01 October 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER